




Is it ‘gene therapy’?

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What, exactly, is ‘gene therapy’? Commissioner Scott Gottlieb of the U.S. Food and Drug Administration’s (‘FDA’s’) recently announced his agency’s intent to develop an expedited approval pathway for ‘gene therapy’ despite the lack of any precise definition by regulators or scientists.^{1,2} At least 25 new therapeutic products have billed themselves as ‘gene therapies’, including several treatments—notably, adenovirus associated vectors (‘AAV’) and *ex vivo* T-cell therapies—that raise difficult questions as to the contours of the term.^{3,4,5} As of this writing, there are more than 700 active investigational

- ¹ Alex Phillpdis, 25 *Up and Coming Gene Therapies*, May 7, 2018, <https://www.genengnews.com/the-lists/25-up-and-coming-gene-therapies/77901090> [archived at <http://perma.cc/8KNE-3M9J>].
- ² FDA, *Remarks by Commissioner Gottlieb to the Alliance for Regenerative Medicine’s Annual Board Meeting*, May 22, 2018, <https://www.fda.gov/NewsEvents/Speeches/ucm608445.htm> [archived at <http://perma.cc/D9VN-VXSQ>].
- ³ FDA, *Luxturna*, Jan. 17, 2018, <https://www.fda.gov/BiologicsBloodVaccines/CellularGeneTherapyProducts/ApprovedProducts/ucm589507.htm> [archived at <https://perma.cc/YA9H-QYM3>].
- ⁴ FDA, *Yescarta (axicabtagene ciloleucel)*, Nov. 16, 2017, <https://www.fda.gov/BiologicsBloodVaccines/CellularGeneTherapyProducts/ApprovedProducts/ucm581222.htm> [archived at <https://perma.cc/4QDY-W2AX>].
- ⁵ FDA, *Kymriah (tisagenlecleucel)*, Sept. 27, 2017, <https://www.fda.gov/BiologicsBloodVaccines/CellularGeneTherapyProducts/ApprovedProducts/ucm573706.htm> [archived at <https://perma.cc/4EM4-9GQX>].

new drug applications for 'gene therapies'.⁶ And yet, FDA's definition of 'gene therapy' dates back to 1993—ancient history relative to recent advances in the field.^{7,8}

This debate concerning what constitutes 'gene therapy' is important beyond mere semantics. Crystallizing a modern definition of 'gene therapy' has now become critically important on several fronts. Following the recent passage of the 21st Century Cures Act, FDA now relies on the term to give regulatory incentives to sponsors of certain 'regenerative medicines', including 'gene therapies'.^{9,10} NIH Director Francis S. Collins and FDA Commissioner Scott Gottlieb recently announced that Recombinant DNA Advisory Committee ('RAC') approval would no longer be required for 'gene therapy' because 'there is no longer sufficient evidence to claim that the risks of gene therapy are entirely unique and unpredictable'.⁶ And in July 2018 FDA issued six draft guidance documents on 'gene therapy', but none with a substantially new definition.¹¹ The term also carries significant baggage regarding drug pricing, with 'gene therapies' seeming to command higher premiums relative to other advanced biotherapeutics. And the advent of gene-edited *ex vivo* therapies, such as CAR-T, has further complicated the use of the phrase. Ultimately, the difference between calling a therapy a 'gene therapy' and something else is the difference between a slate of regulatory incentives, streamlined approval, specific manufacturing guidances, and, likely, premium prices and public cache.

Today's core difficulty in defining 'gene therapy' lies in categorizing genetic modifications that do not directly modify a pathogenic gene *in vivo*. Autologous cell treatments, for example, do genetically modify patients' own cells, but outside of the body—*ex vivo*.^{2,4} That, under some definitions, is 'gene therapy'. But such therapies impart new genes into cells rather than fix a specific genetic failure. This is not 'gene therapy', in the skeptic's view, because the therapy itself has nothing to do with deficiencies in a patient's genetic makeup.

Properly defining gene therapy is ultimately important for understanding and communicating the state of the science, and for helping regulators tailor and clarify both incentives and requirements for those products appropriately characterized as 'gene therapy'. This is so even as our understanding of what constitutes a 'gene' continues to change. We review the contours of the term here, and propose that 'gene therapy'—in the lay, scientific, and legal sense—should be defined as an intentional and expected permanent alteration of a specific DNA sequence of the cellular genome—that is, the sum of DNA that exists within a cell—for a clinical purpose. We also propose that gene therapy, as we define it, can be further categorized into at least three types: direct,

⁶ Francis S. Collins & Scott Gottlieb, *The Next Phase of Human Gene-Therapy Oversight*, NEW ENGL. J. MED. (Aug. 15 2018).

⁷ FDA, *What is Gene Therapy?*, Jan. 9, 2018, <https://www.fda.gov/BiologicsBloodVaccines/CellularGeneTherapyProducts/ucm573960.htm> [archived at <https://perma.cc/WY6A-CNTM>].

⁸ FDA, Application of current statutory authorities to human somatic cell therapy products and gene therapy products. 58 Fed. Reg. 53248–53251 (Oct. 14, 1993).

⁹ 21st Century Cures Act, 144 Pub. L. 255, 130 Stat. 1033 (2016).

¹⁰ FDA, Draft Guidance, Expedited Programs for Regenerative Medicine Therapies for Serious Conditions, Nov. 2017, <https://www.fda.gov/downloads/biologicsbloodvaccines/guidancecomplianceregulatoryinformation/guidances/cellularandgenetherapy/ucm585414.pdf> [archived at <https://perma.cc/EZ23-QR8G>].

¹¹ Zachary Brennan, *FDA Unveils 6 New Draft Guidances on Gene Therapy*, REGULATORY FOCUS, July 11, 2018, <https://www.raps.org/news-and-articles/news-articles/2018/7/fda-unveils-6-new-draft-guidances-on-gene-therapy> [archived at <https://perma.cc/4GVG-ZHKM>].

compensatory, and augmenting. Defining gene therapy in this fashion would provide clarity to scientists and regulators alike.

PRIOR ATTEMPTS TO DEFINE 'GENE THERAPY'

Since Watson and Crick's discovery of the molecular structure of DNA, the 'Holy Grail' of molecular biology has been the ability to precisely edit the genome of in living tissue.¹² The functional idea behind this aspiration is that by replacing some of a body's genetic material, researchers and clinicians can effectively reprogram genetic illnesses. But underlying this goal lies a deep-philosophical line-drawing problem: all therapies, in some sense, affect a patient's genes, whether it's through altering transcription, regulating translation, or even modifying the epigenome. A relaxing vacation—sun, surf, and sangria—arguably does more to regulate gene expression than many 'precision' therapies.

Beginning in the 1970s, scientists attempted to cabin gene therapy with a concrete, practical definition. In a 1972 article in *Science*, Ted Friedmann and Richard Roblin first proposed that a definition of 'gene therapy' required 'exogenous "good" DNA be used to replace the defective DNA in those who suffer from genetic defects'.¹³ But, as Friedmann and Roblin noted, the time's 'understanding of such basic processes as gene regulation and genetic recombination in human cells [was] inadequate' to make trials ethical.¹¹ This did not, however, prevent some unauthorized trials in humans shortly thereafter.¹⁴ By 1986, molecular biology had progressed enough to convene a meeting of the Institute of Medicine (IOM) to propose the first likely 'gene therapy' candidates, with a focus on 'gene therapy' as the addition or replacement of a gene in a targeted, somatic cell type.¹²

In the same year, FDA finalized its position that it has jurisdiction over—and would subject to regulatory approval—human gene therapy, albeit without clearly defining the term. Stakeholders' requests for more guidance from the agency, as well as continued advances in the science, eventually led FDA, in 1993, to define 'gene therapy' in an official Notice that aimed to clarify the FDA's overall regulatory approach. Gene therapies are those used to 'modify or manipulate the expression of genetic material or to alter the biological properties of living cells'¹⁵—a definition broad enough to cover any treatment and seemingly intended to ensure FDA retained oversight over a then fast-moving technology. FDA recently reiterated this definition in draft guidance issued in July 2018, adding that gene therapies are those 'products that mediate their effects by transcription or translation of transferred genetic material or by specifically altering host (human) genetic sequences'.¹⁵ In its 1993 Notice, FDA also distinguished 'gene therapy' from 'somatic cell therapy'—cells 'propagated, expanded, selected, pharmacologically treated, or otherwise altered' for therapeutic purposes—a definition significantly overlapping with that of 'gene therapy'.⁷ Others suggested abandoning the term

¹² Giedrius Gasiunas & Virginijus Siksnys, *RNA-Dependent DNA Endonuclease Cas9 of the CRISPR System: Holy Grail of Genome Editing?* 21 *TRENDS MICROBIOL.* 562–67 (2013).

¹³ Theodore Friedmann & Richard Roblin, *Gene Therapy for Human Genetic Disease?* 175 *SCIENCE* 949–55 (1972).

¹⁴ Mule J. Cline, *Gene Therapy: Current Status*, 83 *AM. J. MED.* 291–97 (1987).

¹⁵ FDA, *Cellular & Gene Therapy Guidances*, July 20, 2018, <https://www.fda.gov/biologicsbloodvaccines/guidancecomplianceregulatoryinformation/guidances/cellularandgenetherapy/default.htm> [archived at <https://perma.cc/4QAD-VSFD>].

'gene therapy' altogether in favor of 'gene transfer' to avoid implying that the unproven interventions provided clinical benefit.

Attempts to define 'gene therapy' waned after the 1999 death of Jesse Gelsinger, a clinical trial subject who succumbed to complications arising from the viral vector used to repair a congenital enzymatic deficiency.¹⁶ After his death, the term 'gene therapy' took on a more negative connotation as a dangerous and unproven technology.¹³ But the advent of newer genetic engineering technologies—such as CAR-T and CRISPR—has refreshed perceptions over gene therapy's possibilities. CRISPR, especially, has ignited the public imagination over a safe, easy, and practicable form of gene therapy.¹⁷

DEFINING 'GENE THERAPY' TODAY

Prior definitions of gene therapy are problematic for several reasons. First, several definitions—such as Friedmann & Roblin's and the IOM's 1986 definition—required the replacement of somatic DNA with exogenous DNA. Modern biotechnologies, however, can alter a cell's genome without either replacing or modifying somatic DNA. Stably transfected AAV therapy, such as Luxturna (voretigene neparvovec-rzyl), adds to the cellular genome without modifying any endogenous sequences.² And some variations of CRISPR can edit somatic DNA without the need for exogenous genetic material.¹⁸ Second, other definitions of gene therapy—such as FDA's—are so broad as to be essentially meaningless. FDA's definition of 'gene therapy' requires merely a modification of genetic expression—a feature of almost all small molecule drugs, as well as food, drink, sleep, and much else. Further, 'gene transfer' is too narrow of a term—one may alter the human genome without transferring a gene to the target, such as through single-base, or even multiple-base gene-editing, as is frequently the case using CRISPR.

Given these recent advances, we propose defining human 'gene therapy' as the intentional, expected permanent, and specific alteration of the DNA sequence of the cellular genome, for a clinical purpose. Our definition requires only that the modification is expected to persist in the cell during its life, not that it is irreversible. Genetic modifications lost over time, such as the loss of transfected episomes, would not be permanent.¹⁹ Further, our definition is agnostic as to whether such modification takes place inside patient's body or, as with CAR-T, outside of it. It is also agnostic as to vector. Indeed, for these reasons, we think our definition encompasses the historical thrust of gene therapy toward novel delivery approaches, including recent and potentially future developments in biotechnology. It is also flexible: While our definition centers on somatic gene therapy, it would equally apply to germline therapy—should it ever come to fruition—as well. Our definition would also include therapies that for reasons typically having to do with dosing, would require multiple deliveries—so long, of course, as a single course of treatment is expected to be permanent. Finally, we believe that because

¹⁶ Jennifer Couzin & Jocelyn Kaiser, *As Gelsinger Case Ends, Gene Therapy Suffers Another Blow*, 307 SCIENCE 1028b (2005).

¹⁷ Thomas Gaj, Charles A. Gersbach & Carlos F. Barbas, III, *ZFN, TALEN, and CRISPR/Cas-Based Methods for Genome Engineering*, 31 TRENDS BIOTECH. 397–405 (2013).

¹⁸ Nicole M. Gaudelli et al., *Programmable Base Editing of A•T to G•C in Genomic DNA Without DNA Cleavage*, 551 NATURE 464–71 (2017).

¹⁹ Anja Ehrhardt, Hui Xu & Mark A. Kay, *Episomal Persistence of Recombinant Adenoviral Vector Genomes During the Cell Cycle in Vivo*, 77 J. VIROL. 7689–95 (2003).

Table 1. Subsidiary categories of gene therapy.

Type of Gene Therapy	Definition	Example
Direct	The intentional modification of a specific somatic gene in order to correct defective genes or to fix an allele's malign function.	Single-base pair editing to resolve insertions or deletions that lead to defective proteins.
Compensatory	The induction of expression of genetic material that compensates for lost or aberrant cellular function.	Editing of gene to increase or decrease expression in target cell, or induce expression normally turned off.
Augmenting	The introduction of a novel function that would not otherwise be present in the target cell type.	Editing of a gene to provide a different function from what is typical; insertion of a new version of a gene into the genome (as opposed to editing the existing version)

our definition requires the intent to alter a specific gene, it best resolves many of the philosophical issues inherent in distinguishing true gene therapy from other therapies that have an incidental effect on gene expression without altering genetic sequences.

Our definition of gene therapy is susceptible to further characterization. We propose that gene therapy, as we define it, can be grouped into at least three subsidiary categories: direct, compensatory, or augmenting (Table 1). Direct gene therapy constitutes the intentional modification of a specific somatic gene to correct defective genes or to fix an allele's malign function, such as the modification of defective blood factor genes associated with hemophilia, or the repair of *CFTR* gene as a cure for cystic fibrosis. Compensatory gene therapy, by contrast, induces the expression of related genetic material that compensates for some lost or aberrant cellular function. One current attempt is the inducement—and permanent expression of—fetal hemoglobin to cure sickle cell anemia and β -thalassemia.^{20,21} Lastly, augmenting gene therapy introduces, again through the stable transfection of genetic material, a novel function that would not otherwise be present in the target cell type. This includes several anti-cancer treatments that insert genetic material encoding synthetic immunoreceptors as a method to augment immune function against tumors.²²

We offer a few observations in support of our definition's value. First, it resolves the status of three recently approved therapies that once strained the definition of 'gene therapy', Luxturna, Kymriah (tisagenlecleucel), and Yescarta (axicabtagene ciloleucel). All concern some expected permanent change to a cell's genome, whether *ex vivo* or

²⁰ Chiara Antoniani et al., *Induction of Fetal Hemoglobin Synthesis by Crispr/Cas9-Mediated Disruption of the β -globin Locus Architecture*, 128 BLOOD 321 (2016).

²¹ Alessia Finotti et al., *Recent Trends in the Gene Therapy of β -thalassemia*, 6 J. BLOOD MED. 69–85 (2015).

²² Francisco J. Sánchez-Rivera & Tyler E. Jacks, *Applications of the CRISPR–Cas9 System in Cancer Biology*, 15 NAT. REV. CANCER 387–95 (2015).

in situ. Changes to genetic coding or expression that, for whatever reason, will revert back to their prior state in the absence of continued therapy are unlikely to be considered 'gene therapy'; they are not permanent and in that sense are no different from therapies or other stimuli that merely have an incidental effect on gene expression. Second, despite our labeling of these treatments as 'gene therapy', none fit within the classical—and, we think, outdated—definition of gene therapy as the direct alteration of a 'defective' nuclear gene. To that end, we believe our definition better aligns the concept of 'gene therapy' to currently used technologies. Third, therapies that permanently alter DNA sequences within the cellular genome, but do so in a haphazard or unknown fashion—as with some carcinogens—should not be considered gene therapy; they fail our intent requirement. Lastly, all three examples concern modifications to a *patient's* cells. Modification of cells that originally did not derive from the same patient—even if those cells are human cells—should, too, not be construed as 'gene therapy' any more than organ transplantation, which transplants the donor's genome, or the genetic modification of a patient's microbiota, should be. These, instead, would be forms of 'tissue' or 'cell therapy'.

We believe our definition of 'gene therapy' is a significant improvement over prior attempts. FDA's current definition, for example, would include nonpermanent oligonucleotide therapy—like RNAi therapies—that are decidedly not 'gene therapy'.²³ Our definition encompasses but moves beyond older conceptions of gene therapy that require the direct editing of a pathogenic variant of particular gene. That definition, by contrast, has proven too narrow. The somatic editing of a benign transcription factor or the insertion of an exogenous gene to improve the functioning of a different gene would fail to be considered gene therapy under these older definitions. Again, we think these criticisms of current definitions of gene therapy illuminate the fundamental characteristics of true 'gene therapy' in both the scientific and legal sense: the permanent modification or addition of the DNA sequence within a patient's own cells. Furthermore, our characterizations of gene therapy into discrete types—direct, compensatory, and augmenting—would allow regulators to particularize the different safety and efficacy concerns involving each type. For example, labeling a gene therapy as either direct or compensatory—where little recombinant DNA is involved—may very well give credence to FDA's and NIH's recently announced intention to forgo RAC review.⁶ But recognizing a gene therapy as augmenting—where novel genetic material imparts a new function to patients' cells—may call for 'using the RAC as an advisory board on today's emerging biotechnologies'.⁶

Under our definition, we also think it is important to clarify what our definition of gene therapy does not do. Our definition is not specific to either vector or mechanism. Regarding vector, genetic modification effected by virii, lipid nanoparticles, or cells should all still be considered genetic therapy. We see no reason why one vector should fall within the confines of gene therapy but another should not; the genetic and functional modification of the genome remains the same. Similarly, we see no reason why one mechanism of editing—assuming its permanency—should constitute gene therapy over any other. The darling of current gene-editing efforts, CRISPR, could be used in our definition of gene therapy equally well as others, such as TALENs, zinc-finger

²³ Teresa Coelho et al., *Safety and Efficacy of RNAi Therapy for Transthyretin Amyloidosis*, 369 NEW ENGL. J. MED. 819–29 (2013).

nucleases, and simple homologous repair mechanisms. For our definition's purposes, gene therapy can be effected using any vector.

Finally, our definition provides room for further change and growth within its scope. Today, we can categorize gene therapies as direct, compensatory, and augmenting—but there are likely more ways of altering the cellular genome than dreamt of in our philosophies. Should another therapeutic approach emerge that changes the DNA sequence of the cellular genome, we would not object to forming new categories of gene therapy so long as it is intentional, expected to be permanent, and specific.

CONTEMPORARY APPLICATION: CAR-T

With our definition of gene therapy in hand, we can more closely examine one philosophically difficult therapy—CAR-T—as an example of how our definition can work robustly in application. One CAR-T therapy, Kymriah, for example, works by removing some of a patient's white blood cells; editing the cells to recognize and target leukemic B-cells; and reinserting the edited cells back into the patient in the hopes of using the modified cells' T-cell receptors and the body's own immune system to destroy leukemic cells. In particular, the patient's cells are modified to express a recombinant targeting molecule—a T cell, with a synthetic chimeric antigen receptor.⁴ That modification—a type of augmenting gene therapy in our classification—makes Kymriah the first in a class of novel therapies known as 'CAR-T'. Upon Kymriah's approval, there was heated debate among the press and public about whether CAR-T was, in fact, 'gene therapy', 'cell therapy', or both,²⁴ an important distinction for both regulators and insurers.

So, is CAR-T 'gene therapy'? On balance, we think 'yes'. CAR-T permanently modifies a patient's own cells *ex situ* and returns those cells to the patient. The modification is directed to a specific fragment of genes associated with T-cell receptor protein chains—an expected permanent alteration for the life of those cells. And the specific modification made—the precise sequence of the transfected genetic material—is intentional. These facets would appear to make CAR-T 'gene therapy'. The initial extraction of cells from the patient is unimportant; our definition would be the same if the same result were achieved *in vivo* through the use of a viral vector. In both cases, a specific gene in a patient's own cells has been intentionally and permanently modified.

Nonetheless, we should note that we do not disagree with Kymriah's simultaneous characterization as 'cell therapy'. The term 'cell therapy'—both in FDA's definition and elsewhere—refers to the therapy's vector, ie cells, as opposed to the therapy's function. Again, our definition of 'gene therapy' is agnostic as to vector. In such instances, some therapies may very well be both cell therapy *and* gene therapy. This is, we believe, no different from referring to a therapy—such as Luxturna—as both viral therapy and gene therapy. Indeed, this is precisely the type of gene therapy originally contemplated by the IOM in 1986: *ex situ* ablative bone marrow gene therapy using viral vectors.¹² Our definition is robust in that it both encompasses easy cases from decades ago and current therapies today.

²⁴ Melissa Healy, *Hailing a Breakthrough in Fighting Cancer, FDA Approves Gene Therapy that Functions as a 'Living Drug'*, LOS ANGELES TIMES, Aug. 30, 2017, <http://www.latimes.com/science/sciencenow/la-sci-sn-car-t-cancer-drug-20170830-htmstory.html> [archived at <https://perma.cc/RV8C-Z8BF>].

CONCLUSIONS

Crafting a modern definition of 'gene therapy' is not merely an exercise in semantics—it's important for regulators, scientists, and the public. A workable definition serves as a good marker for whether we have successfully found a broad version of molecular biology's 'Holy Grail'. Until we can stably, permanently, and intentionally alter any genes of our choosing in living patients, we think it fair to say that we have yet to succeed in that goal. Better defining gene therapy also provides more regulatory clarity than currently exists. Understanding that determining whether something constitutes 'gene therapy' is independent of vector suggests that the *overall* safety and efficacy of the editing process, rather than the nature of the vector, should be the primary focus of regulation. That is, our definition of gene therapy makes clear that the safety and efficacy of gene therapy means the safety and efficacy of the edits themselves are of a different nature than narrower issues for the vector chosen. We also hope that crystalizing a definition of gene therapy would improve the public's understanding of an otherwise scientifically difficult term. On a broader level, concretely defining gene therapy allows us to benchmark progress in clinical molecular biology as advances pass through proofs of concept and ultimately regulatory review. At the very least, we expect our definition to be a focus for discussion about what 'gene therapy' means and why definitions are important.

AUTHOR CONTRIBUTIONS

JSS, PJZ, and HTG collaboratively conceptualized and wrote the article.

SUPPLEMENTARY DATA

Supplementary data are available at [JLBIOS](https://academic.oup.com/jlb/article/5/3/786/5078563) online.